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## THE EFFECT OF THORIUM X ON ACTIVE ANAPHYLAXIS IN THE GUINEA-PIG

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It has been suggested that the greater part of the difference between tuberculosis in children and in adults is explicable on the basis of an allergic condition in the adult. Early in his work Koch recognized that an animal injected with tubercle bacilli reacted distinctly differently locally after the second injection than after the first.<sup>1</sup> It also seems well established that the chronic cavity and fibroid type of tuberculosis is the reaction of a resistant organism while the rapidly progressive military type is the result of invasion in a highly susceptible organism. It was with a view to obtain information in regard to the significance of the allergic condition with respect to the local reaction to tubercle bacilli and to the systemic susceptibility that the following experiments were made.

It was thought that if it was possible by some means to reduce the allergic condition in guinea-pigs such animals would reveal marked differences in their reactions as compared with allergic animals not thus treated.

The results of the work by v. Heinrich<sup>2</sup> and by Schiff<sup>3</sup> indicated that the proposed plan for determining the importance of allergy in tuberculosis would be feasible. By means of the roentgen ray v. Heinrich was able markedly to influence the formation of "sensibilisin." Using diphtheria antitoxin (horse serum) as the protein solution, and giving 0.01 c c for sensitizing and from 0.05-0.5 c c as intoxicating doses, he found that one erythema dose (3 Kaloms) of roentgen ray given any time within 14 days after the sensitizing dose, the intoxicating dose given three weeks later, would so influence the lymphoid tissues that, as he believed, antibody formation was interfered with and thus also the formation of the anaphylactic poison. The greatest effect was noted coincidentally with the maximum effect on the lymphoid tissues. Roentgenization immediately before the intoxicat-

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<sup>1</sup> Corper, H. J.: *Am. Rev. Tuberculosis*, 1917, 1, p. 407.

<sup>2</sup> *Centralbl. f. Bakteriol.*, I, O., 1913, 70, p. 421.

ing dose was without effect. In experiments on passive anaphylaxis, the roentgenized guinea-pig serum conferred no sensitiveness on the recipient, in contradistinction to the serum of untreated animals, thus demonstrating further the absence of antibody formation. He suggested that the experiments would be made better with thorium X, but was unable to obtain any. Peptone shock — differing from anaphylactic shock — was not influenced by roentgenization. He believes with Seligmann<sup>4</sup> that inability to passively transfer anaphylaxis from tuberculous guinea-pigs is due to the large amount of destruction of lymphoid tissue suffered by such animals. Schiff,<sup>3</sup> realizing that benzene, on account of its destructive action, was not as suitable as the roentgen ray, tried its effect on anaphylaxis produced by sheep serum, 0.02 c c subcutaneously for sensitizing and from 0.001-0.02 for intoxicating on the 18th day. The benzol was given in doses of 0.01 c c intraperitoneally, 7 injections at 4-day intervals, and of 0.03 c c intraperitoneally, 8 injections at 2-day intervals. The fatal doses of intoxicating protein was the same in the treated and untreated guinea-pigs. Differences were noted only on the border line, 57% of the small dose benzene animals and 17% of the controls dying, while 17% of the large dose benzene animals and 71% of the controls died. He believed the increased or diminished susceptibility to be due to the influence of the benzene on the tissues that form antibodies; that is, the hematopoietic system, and concludes that benzene influences the anaphylactic reaction in actively prepared animals, small doses of benzene increasing the susceptibility and large doses diminishing it.

On account of the availability, regulation of dosage, and administration, thorium X was used in the experiments now reported. Thorium X is easily administered in 0.9% sodium chlorid solution, is not influenced by boiling and its strength is easily and quickly determined by means of a simple electroscope.<sup>5</sup> The radio-thorium from which the thorium X was prepared for use was contributed by Dr. Herbert N. McCoy, Carnotite Reduction Co., Chicago.

For comparison, three separate protein mixtures, egg white, normal horse serum and milk were used for producing anaphylaxis. The thorium X was given at different intervals before and after sensitiza-

<sup>3</sup> Zeitschr. f. Immunitätsf., 1914-15, 23, p. 61.

<sup>4</sup> Zeitschr. f. Immunitätsf., 1912, 14, p. 419.

<sup>5</sup> Corper, H. J.: Am. Rev. Tuberculosis, 1918, 2, p. 587.

TABLE 1  
THE EFFECT OF THORIUM X ON ANAPHYLAXIS BY EGG WHITE

Experiments	Thorium X		Maxi- mum Reac- tion	Time of Maxi- mum Reac- tion	Lowest Leuko- cyte Count	Time in Days of Lowest Leukocyte Count		Leuko- cyte Count on Day of Second Protein Injec- tion
	Dose in Units	Administration				After Sensi- tiza- tion	After Injec- tion Thori- um X	
Series I Expers. 1, 2, 3	0		Died	20"	7,750			8,250
			Died	20"	13,000			15,250
			Died	25"	8,250			8,500
Single large injection of Thorium X with sensitizing injection. Expers. 4, 5	35	With 1st (sensitizing) injection of protein	Died	30"	1,500	14	14	2,500
			Died	25"	1,250	13	13	2,100
Leukocytes maintained low throughout entire incubation period. Expers. 6, 7, 8, 9	3 to 5	Injections begun 4 days before 1st injection of protein and repeated daily or every second day as necessary.	Died	27"	2,150	17		2,250
			Died	42"	1,500	18		1,750
			Died	50"	1,625	17		2,000
			Died	36"	1,250	19		1,250
Small repeated injections of Thorium X. Expers. 10, 11, 12	0.1	Injections begun 3 days before first protein injection and repeated every third day throughout	Died	20"	7,500	10		8,750
			Died	40"	5,250	17		7,000
			Neg.		7,750	12		8,500
Single large injection of Thorium X 7 days before second protein injection. Expers. 13, 14, 15	35	Single injection 7 days before second protein injection	Died	35"	2,500	19	7	2,500
			Died	25"	1,250	18	6	1,500
			Died	30"	2,000	17	5	2,100
Series II Expers. 16, 17, 18	0		Died	15"	10,000			10,500
			Died	20"	8,750			9,500
			Died	20"	8,000			8,000
First injection protein given when leukocytes were low. Expers. 19, 20	40	Single large injection 6 days before first protein injection	Died	20"	1,250	4	10	5,000
			Died	20"	1,000	5	11	5,000
Single large injection of Thorium X given with second protein injection. Expers. 21, 22, 23	40	Single large injection with second protein injection	Died	20"	8,000			8,750
			Died	15"	8,750			10,000
			Died	25"	7,250			8,750

Series I includes animals 1-15 in which the interval between the first and second injection of egg white was 19 days. Series II includes animals 16-23 given the same dose of egg white [0.1 cc with 0.1 cc of distilled water intraperitoneally for the first (sensitizing) injection and 1 cc plus 1 cc of distilled water intraperitoneally for the second (intoxicating) injection], but the interval between the first and second injection of egg white being 17 days.

A unit is an arbitrary index of the amount of Thorium X that will completely discharge an electroscope of certain type in one minute.<sup>5</sup> Expressed in lethal doses 100 units are fatal to a guinea-pig about 400-600 gm. in weight in 15 days while 50 units are not lethal, 250 units kill in 10 days, 500 in 7 days and 1,000 in 6 days.

tion, and before and with the second (intoxicating) dose of protein, and in different amounts. Daily leukocyte counts were made to note the effect of the thorium X and the relation between the number of circulating leukocytes and anaphylaxis. The experiments with egg white, prepared by mixing fresh egg white with an equal volume of sterile distilled water and filtering, all resulted in fatal anaphylaxis so that only the inhibitory effect of the thorium X, if such occurred, could be noted. The results are given in table 1.

It is to be noted that thorium X in large doses, given before (6 days) or coincident with the sensitizing injection of egg white, or before (7 days) or with the second injection, had no appreciable effect on the fatal anaphylaxis from the second injection of egg white. Likewise, repeated injection of thorium X sufficient to maintain a leukopenia as low as 2,000 leukocytes per c mm of peripheral blood throughout the incubation period, or very small repeated injections not appreciably affecting the peripheral leukocytes, had just as little effect on the anaphylactic shock from the second injection of egg white.

The second set of experiments in which normal horse serum was used resulted in less severe anaphylactic symptoms on the second injection of the serum in the controls and therefore was more suitable for determining slight effects on anaphylaxis by the thorium X. Examination of table 2, however, reveals no consistent effect of the thorium X on the severity of the anaphylaxis by the normal horse serum. It seems that, if anything, the thorium X treated animals were more severely affected by the second protein injection than the controls.

In the experiment with milk protein the results of the second injection were not fatal, and thus permitted notation of slight variation in the anaphylactic reaction as affected by the thorium X (table 3).

As a whole the experiments with milk protein are corroborative of those with normal horse serum in that thorium X in large doses given before (7 days) or coincident with the first injection of milk or before 8 days, or with (5 hours before) the second injection had no appreciable effect on the severity of the anaphylaxis. Likewise repeated injection of thorium X, sufficient to maintain a leukopenia as low as 2,000 per c mm of peripheral blood throughout the interval of 16 days, between the first and second injection of milk, or very small repeated injections not appreciably affecting the peripheral leukocytes had just as little effect on the severity of the anaphylactic symptoms.

TABLE 2  
THE EFFECT OF THORIUM X ON ANAPHYLAXIS BY NORMAL HORSE SERUM

Experiments	Thorium X		Maxi- mum Reac- tion	Time of Maxi- mum Reac- tion	Lowest Leuko- cyte Count	Time in Days of Lowest Leukocyte Count		Leuko- cyte Count on Day of Second Protein Injection
	Dose in Units	Administration				After Sensi- tiza- tion	After Injection Thorium X	
Series I Expers. 1, 2, 3	0		+	1'	6,000			7,750
			+	1'	9,500			9,500
			+++	1'	6,250			7,250
Single large injection of Thorium X with sensitizing injection. Expers. 4, 5, 6	35	With first injection of protein	Died	45"	1,500	9	9	4,250
			Died	25"	1,125	9	9	2,750
			++	1'	2,350	8	8	4,000
Leukocytes maintained low throughout entire incubation period. Expers. 7, 8, 9	3 to 5	Injections begun 4 days before first injection of protein and repeated daily or every second day as necessary	+++	1' (dead 26')	1,500	9		1,600
			Died	2'	1,250	15		1,300
			+++	1'	1,250	15		1,600
Small repeated injections of Thorium X. Expers. 10, 11, 12	0.1	Injections begun 3 days before first protein injection and repeated every third day throughout	Died	45"	5,250	13		6,000
			++	30"	8,000	11		8,500
			++	1'	6,250	10		8,000
Single large injection of Thorium X 7 days before second protein injection. Expers. 13, 14, 15	35	Single injection 7 days before second protein injection	++	40" (died 18')	1,000	19	7	1,000
			+++	30" (died 36')	750	19	7	750
			Died	1¼'	750	19	7	750
Series II Expers. 16, 17, 18	0		+++	45"	8,000			8,750
			+++	45"	7,500			8,750
			+++	45"	7,000			7,750
The first injection of protein given when leukocytes were low. Expers. 19, 20, 21		Single large injection 6 days before first protein injection	+++	1'	1,000	2	8	5,000
			+++	1¼'	1,250	3	9	4,750
			+++	45"	1,000	2	8	5,500
A single large injection of Thorium X given with second injection of protein. Expers. 22, 23, 24	40	Single large injection with second protein injection	++	30"	7,250			8,000
			Died	50"	6,250			7,500
			Died	1½'	7,500			10,000

Series I includes animals 1-15 in which the interval between the first and second injection of normal horse serum was 19 days. Series II includes animals 16-24 given the same dose of normal horse serum [0.1 cc with 0.1 cc of distilled water intraperitoneally for the first (sensitizing) injection and 1 cc with 1 cc of distilled water intraperitoneally for the second (intoxicating) injection] but the interval between the first and second injection of horse serum being 17 days.

The reactions are graded into mild +, moderate ++, and severe +++ with subsequent recovery of the animal.

TABLE 3  
THE EFFECT OF THORIUM X ON ANAPHYLAXIS BY MILK PROTEINS

Experiments	Thorium X		Maximum Reaction	Time of Maximum Reaction	Lowest Leuko-cyte Count	Time in Days of Lowest Leukocyte Count		Leuko-cyte Count on Day of Second Protein Injection
	Dose in Units	Administration				After Sensitization	After Injection Thorium X	
Controls. Expers. 1 and 2	0		+++	45"				
			+++	1'				
First injection of protein given when leukocytes were low. Expers. 3, 4	40	Single large injection 7 days before the first protein injection	++	45"	1,750	0	7	6,250
			+++	1'	1,000	4	11	4,500
Single large injection of Thorium X with sensitizing injection. Expers. 5 and 6	40	With first injection of protein	+++	1'	1,250	8	8	3,750
			++	30"	1,250	12	12	4,500
Leukocytes maintained low throughout entire incubation period. Expers. 7, 8	5-10	Injections begun 7 days before first protein injection and repeated as necessary	++	45"	2,500	0		2,750
			+++	45"	1,250	6 and 12		2,250
Small repeated injections of Thorium X. Expers. 9, 10, 11	0.1	Injections begun 2 days before the first protein injection and repeated every third day throughout	+++	45"	6,250	10		7,000
			+++	45"	7,750	12		8,000
			+++	30"	7,250	9		7,500
Single large injection of Thorium X before the second protein injection. Exper. 12, 13, 14	40	Single injection 8 days before the second protein injection	+++	1'	1,250	15	7	1,500
			++	30"	2,300	16	8	2,400
			+++	30"	2,500	16	8	2,500
A single large injection of Thorium X given with the second injection of protein. Expers. 15, 16	40	Single large injection 5 hours before second protein injection	+++	1'	5,000			6,500
			+++	1½'	6,750			8,000

The guinea-pigs in this experiment all received 0.5 cc of milk for the first injection intraperitoneally and 5 cc of milk for the second injection intraperitoneally, the interval between the injections being 16 days.

In order to note whether there was any direct relation between the size of the dose of thorium X or the leukocyte level in the peripheral blood and the severity of the symptoms, a series of guinea-pigs were given different amounts (from 1-500 units) of thorium X seven days before the second protein injection. Normal horse serum was used as the protein mixture because the results obtained with it allowed of notation of variations of either an inhibitory or enhancing influence

(table 4). In interpreting these results, it is to be borne in mind that 100 units of thorium X are lethal to a guinea-pig in 15 days, 250 units in 10 days, 500 units in 7 days, and 1,000 units in 6 days; thorium X acting as a chronic poison; 50 units are nonlethal.

TABLE 4  
EFFECT OF DIFFERENT AMOUNTS OF THORIUM X AND OF DIFFERENT LEUKOCYTE LEVELS ON  
ANAPHYLAXIS BY NORMAL HORSE SERUM

	Thorium X Dose in Units	Maximum Reaction	Time of Maxi- mum Reaction	Lowest Leukocyte Count	Time in Days of Lowest Leukocyte Count		Leukocyte Count on Day of Second Protein Injection
					After Sensi- tiza- tion	After Injection of Thor- ium X	
1 2 3	0	+++ +++ +++	1' 45'' 45''				
4 5	1	Died Died	1'10'' 1'25''	5,000 4,500	16 16	5 5	5,500 5,000
6 7	2	Died ++	2' 15''	4,000 4,500	15 16	4 5	4,750 5,000
8 9	5	+++ +++	45'' 45''	2,500 1,500	18 16	7 5	2,500 2,500
10 11	10	+++ ++	45'' 45''	3,250 2,500	18 16	7 5	3,250 2,500
12 13	20	+++ ++	1' 45''	1,250 1,750	17 18	6 7	1,500 1,750
14 15	50	+++ ++	45'' 45''	2,500 1,750	16 17	5 6	3,000 1,750
16 17	100	Died +++ (Died 24')	2½' 2'	1,000 750	17 16	6 5	1,500 1,000
18 19		++ (Died 2 days) +++ (Died 5')	1' 2'	500 500	18 18	7 7	500 500
20 21	500	++ (Died 5') +++ (Died 18')	2' 2'	500 500	18 17	7 6	500 500

The thorium X was injected intraperitoneally 7 days before the second protein injection was given, and the interval between the first and second protein injection was 18 days.

With the exception of the animals given one unit, in which case the results are unexplained—Schiff found small doses of benzene to increase the severity of the reaction—and those given lethal doses of thorium X, the results are fairly uniform in that they indicate that thorium X *per se* or the number of leukocytes found in the peripheral blood have no influence on the symptoms produced in guinea-pigs by the second injection of horse serum. When a lethal dose of thorium X had been given the second injection of horse serum simply hastened death probably because of the combined action of two poisons—thorium X and anaphylatoxin.



## DISCUSSION

The object of these experiments was to obtain a method applicable to the study of one of the problems in tuberculosis — that of allergy. In this the method planned proved impractical. Although the experiments were not planned to give slight differences, they seem to have been of sufficient accuracy to indicate either that the roentgen ray and benzene act differently from thorium X or that the observations with the roentgen ray and benzene are incorrect and require corroboration. The work should be repeated, using the roentgen ray, benzene and thorium X at the same time, and with a large series of animals to rule out accidental differences.

## SUMMARY

Thorium X given in about  $\frac{1}{2}$  the lethal amount seven days before or coincident with the primary injection of egg white, normal horse serum or milk proteins, or 7 days before or with the second injection of these proteins had no appreciable effect on the severity of the anaphylactic symptoms in guinea-pigs on reinjection of protein 16 to 18 days after the primary injection. Likewise, the repeated administration of smaller doses of thorium X sufficient to maintain a leukopenia as low as 2,000 leukocytes per cmm throughout the entire interval of 16 to 18 days between the first and second injections, or very small repeated injections not appreciably affecting the number of peripheral leukocytes, had just as little effect on the severity of the anaphylactic symptoms.

There was no direct relation noted between the anaphylactic symptoms and the leukocyte counts as affected by thorium X. In the larger doses the effect observed seemed to be due to the combined action of two toxic substances — the thorium X, a chronic poison, and the anaphylatoxin, an acute poison.